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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	9

DATE MAILED: 02/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/928,262	HAVENGA ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,24-25,27,and28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892) ✓
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) ✓
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claims 1-11, 24-25, and 27-28 are pending examination.

The cancellation of claims 11-23 and 26 and the amendment to claims in paper no. 8 is acknowledged and considered.

Noncompliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

If the applicants do not comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures in the response to this office action, the response will be considered non-responsive.

Applicant's election without traverse of Group I (claims 1-11,24-25,27-28) and species one deletion in the E3 region and species fiber derived from adenovirus 35 in Paper No. 8 is acknowledged.

The species fiber protein of a B-type adenovirus selected from adenovirus 16 and adenovirus 5 in claim 5 and species in claim 9 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in EPO on 8/10/00. It is noted, however, that applicant has not filed a certified copy of the 002022835.5 application as required by 35 U.S.C. 119(b).

Information Disclosure Statement

The information disclosure statement filed on September 25, 2001 does not fully comply with the requirements of 37 CFR 1.98 because: applicants do not properly cite the abstracts listed on the 1449.

References have been considered by the examiner, but in order to have the abstracts initialed and dated on the 1449, a new 1449 properly citing the abstracts must be filed with the response to this office action. Failure to comply with this notice will result in the above mentioned information disclosure statement being placed in the application file with the non-complying information **not** being considered. See 37 CFR 1.97(i).

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because: the provisional application is listed under prior foreign application. Suggest placing the provisional under the heading "prior provisional application(s)".

Specification

The disclosure is objected to because of the following informalities: on page 4 there is a reference to see Table I, however there is no Table I only Table 1 in the specification.

The specification contains misspelling of the word "aderxovirus" on the bottom of page 7. These and any other, spelling errors should be corrected in response to this office action. Applicant is encouraged to review the specification for additional spelling errors.

Appropriate correction is required.

Claim Objections

Claims 10 and 24 are objected to because of the following informalities: The term "and/or" is grammatically incorrect.

The misspelling of the word "of" in claim 10, line 3.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6-8, 10-11, 24-25, and 27-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3, 6-8, 10-11, 24-25, and 27-28, as best understood, are readable on a genus of a recombinant adenovirus having a tropism for primary chondrocytes, wherein the genus of recombinant adenoviruses is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates production of a genus of a recombinant adenovirus having a tropism for primary chondrocytes. The as-filed specification provides sufficient description of recombinant adenovirus based on a 5 serotype having a tropism for primary human chondrocytes, wherein the tropism is provided by at least a tropism determining part of adenoviral fiber protein of an adenoviral protein of a B-type adenovirus. Furthermore, the as-filed specification and art of record teach that fiber proteins from different adenoviruses differ considerably (Wickham, US 6,455,314, column 1, line 65-cloumn 2, line 55). The claimed genus encompasses using recombinant adenovirus, wherein the fiber protein is not modified or a chimeric adenovirus with a modified fiber protein, wherein the modified fiber protein is from an adenovirus with a different serotype. In addition, the genus encompasses inserting or adding a ligand, antibody, nucleic acid sequence encoding an amino acid sequence with a tropism for primary human chondrocytes or a non-native amino acid sequence (Wickham, US Patent No. 5,846,782) to the fiber protein that is not disclosed in the specification. The claims recite a function (tropism for human chondrocytes), but do not disclose a structure for a representative number of species for the claimed genus of recombinant adenovirus or how to obtain or make a

representative number of species for the claimed genus of recombinant adenovirus having tropism for primary human chondrocytes. In view of the numerous and complex structures encompass by the claimed invention, the specification lacks written description for the claimed genus of recombinant adenovirus.

It is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of recombinant adenoviruses as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of recombinant adenoviruses that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed a genus of a recombinant adenovirus having a tropism for primary chondrocytes. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of recombinant adenovirus that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such

that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of a recombinant adenovirus having a tropism for primary chondrocytes that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1-8, 10-11, 24-25, and 27-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of delivering of delivering a nucleic acid of interest to a primary human chondrocyte *in vitro* comprising infecting the isolated human chondrocyte with a recombinant adenovirus based on adenovirus serotype 5 having a tropism for primary human chondrocyte, wherein said tropism is provided by at least a tropism determining a part of an adenoviral fiber protein of an adenoviral fiber protein of a B-type adenovirus, does not reasonably provide enablement for a method for delivering a nucleic acid of interest to a primary chondrocyte comprising providing a recombinant adenovirus having a tropism for primary human chondrocytes and for a method of inhibiting cartilage disease progression or repairing cartilage in a human using the claimed recombinant adenovirus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possession of a genus of a recombinant adenovirus having a tropism for primary chondrocytes, particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended, e.g. used in a method of delivering a nucleic acid of interest to a primary human chondrocyte.

The claimed invention is directed to making a recombinant adenovirus having a tropism for primary human chondrocytes and using the adenovirus for delivering a nucleic acid to a primary human chondrocytes. More specifically, the claimed invention is directed to using the adenovirus a method of inhibiting cartilage disease progression or repairing cartilage in a human. The invention lies in the field of gene therapy for treating a cartilage disorder in a human.

Furthermore, and with respect to claims directed to any adenoviral vector useful for gene therapy and directed to any treatment of a human; the state of the art exemplified by Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

In addition, gene transduction to chondrocytes has not been well studied (Arai et al. J Rheumatol, Vol. 24, pp. 1787-95, 1997). Many proteins have been reported to protect articular cartilage and are believed to have use as anti-arthritic proteins. However, conventional delivery systems such as oral, intravenous, intramuscular, or intraarticular administration have problems in delivering a drug to a specific joint and maintaining long term therapeutic effect (Arai, page

1787). Arai further states that, "if we can transduce chondroprotective genes into chondrocytes of cartilage, this could be efficient therapy for joint disorders (pages 1787 and 1792)." The art of record further teaches that in vivo methods do not deliver enough genes to chondrocytes in cartilage (Ikeda et al., The Journal of Rheumatology, Vol. 27, pp. 990-6, 2000 and Nixon et al. Clinical Orthopaedics and Related Research, Vol. 379S, pp. S201-213, 2000).

Thus, the state of the art for gene therapy for treating a cartilage disorder is considered unpredictable.

The specification provides examples to illustrate the present invention: Example 1 is the generation of adenovirus serotype 5 genomic 15 plasmid clones. Example 2 is the generation of adenovirus serotype 5 based viruses with chimer fiber proteins. Example 3 is the production, purification and titration of fiber chimeric adenoviruses. Example 4 is testing for the expression on primary chondrocytes for membrane molecules known to be involved n Ad5 infection. Examples 5-7 are adenovirus transduction of human primary human chondrocytes *in vitro*, wherein the adenovirus comprises a marker gene.

In view of the In Re Wands Factors, the as-filed specification only provides sufficient guidance or factual evidence to make and use a recombinant adenovirus based on a 5 serotype having a tropism for primary human chondrocytes, wherein said tropism is provided by at least a tropism determining part of adenovirus fiber protein of a B-type adenovirus. Furthermore, the claims read on using a recombinant or a chimeric adenovirus or replacing the fiber protein with a nucleic acid sequence encoding an amino acid sequence having a tropism for primary human chondrocytes. The art of record and the specification teach that the initial step for successful infection of an adenovirus to its target cell is mediated through the fiber protein. Furthermore,

the specification teaches that although successful introduction of changes in the adenovirus serotype 5 fiber and penton-base have been reported by others, the complex structure of knob and limited knowledge of the precise amino acids interacting with Coxsackie adenovirus receptor (CAR) render such targeting approaches laborious and difficult. The specification does not teach how to use a representative number of recombinant adenovirus having a tropism for primary human chondrocytes, which can assemble in producer cell or packaging cells. In addition, the specification does teach which genes to use in the claimed methods and/or which disease or condition can be treated with any nucleic acid of interest. The art of record teaches that fiber proteins from different adenoviruses differ considerably (Wickham, US 6,455,314, column 1, line 65-cloumn 2, line 55). Thus, it is readily apparent that the as-filed specification fails to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement, e.g. Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997).

The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:
It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.

In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

In view of the art of record, the breadth of the claims, and the lack of guidance provided by the specification, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the generation of chimeric adenoviruses based on a recombinant adenovirus based on a serotype 5 with modified fiber genes to the genus of claimed recombinant adenovirus. Thus, the specification does not enable one skilled in the art to make and use a genus of recombinant adenovirus having a tropism for primary human chondrocytes for use in the claimed methods.

In addition, the specification only provides sufficient guidance for a method of delivering of delivering a nucleic acid of interest to a primary human chondrocyte *in vitro*. The specification does not provide a working example for the claimed method of treating a cartilage disorder using the claimed recombinant adenovirus. The specification does not display how marker gene expression reasonably extrapolates to repairing cartilage in a human or inhibiting cartilage disease progression in a human. The art of record teaches the unpredictability of *in vivo* delivery of a nucleic of interest to a specific cell (chondrocytes) in a human (see Anderson, Verma, Ikeda). The art of record further teaches that *in vivo* methods do not deliver enough genes to chondrocytes in cartilage to generate a therapeutic response for treating a cartilage disorder in a human (see Ikeda). Therefore, the as-filed specification does not provide sufficient description or factual evidence for one skilled in the art to make and use the claimed invention.

Furthermore, with respect to the claims that encompass a recombinant adenoviral vector comprising a specific nucleotide sequence of interest not operatively linked to a promoter. The specification provides sufficient guidance for one skilled in the art to make and use a recombinant adenovirus vector, which expresses a nucleic acid of interest comprising a promoter

operatively linked to the nucleic acid of interest. However, the specification fails to provide sufficient guidance or evidence for one skilled in the art to make and use a recombinant adenovirus, which expresses a nucleic acid of interest comprising a promoter that is not operatively linked to any specific nucleotide sequence in the recombinant adenovirus. The teachings in the specification are directed to using a promoter to express the sequence. The as-filed specification provides guidance or evidence for how to make and use adenoviral vectors comprising a promoter operatively linked to a nucleotide sequence to direct nucleotide expression, however the claims do not recite such a structural limitation. Thus, to the extent the claims fail to recite distinguishing features to commensurate with the level of guidance presented, the claims are not considered enabled.

As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed recombinant adenovirus generates a therapeutic effect, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any nucleic acid therapy method as contemplated by the claims, particularly given the unpredictability of nucleic acid therapy as a whole and/or the doubts expressed in the art of record.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable the for a method of delivering of delivering a nucleic acid of interest to a primary human chondrocyte *in vitro* comprising infecting the isolated human chondrocyte with a recombinant adenovirus based on adenovirus serotype 5 having a tropism for primary human chondrocyte, wherein said tropism is provided by at least a tropism determining a part of an adenoviral fiber

protein of an adenoviral fiber protein of a B-type adenovirus. Given that making a recombinant adenovirus vector comprising a promoter not operatively linked to a nucleotide sequence in the adenoviral vector was unpredictable at the time the invention was made, and given that gene therapy wherein any adenoviral vector is employed to correct a disease or a medical condition in any human was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any gene delivery vector cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicants' disclosure and the unpredictability of gene therapy.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1, 2, 3, 4, 5, 6, 7, and 8 are rejected under 35 U.S.C. 102(e) as anticipated by Wickham et al. (US Patent No. 6,455,314, EFD 9/11/98) or, in the alternative, under 35 U.S.C. 103(a) as obvious over Doherty et al. (Osteoarthritis and Cartilage, Vol. 6, pp. 153-160,

1998). Wickham teaches a method of infecting a chondrocytes comprising administering a recombinant chimeric adenoviral virion incorporating a recombinant fiber protein with appropriate cell-specific ligand (column 4, line 45 - column 10, line 1-45). Wickham further teaches that through fiber incorporation the protein would exhibit reduced affinity for a native substrate than does a wild-type adenoviral fiber trimer and integration of an appropriate cell-specific ligand, the virion can be employed to target any desired cell type including chondrocytes (abstract and column 9, line 20-column 10, line 67). The recombinant fiber protein can be from B-serotype adenovirus 35 (column 4, lines 28-41). In addition, Wickham teaches *in vivo* recombinant adenoviral vector gene delivery, wherein the adenoviral vector comprises a modified fiber protein. The recombinant adenoviral vector would transfect many cells, including chondrocytes. Wickham does not specifically teach infecting human chondrocytes, however, Doherty teaches that human chondrocytes were used in adenovirus vector-gene transduction studies. This teaching shows that one of skill in the art would interpret the chondrocytes of Wickham to be human.

Claims 1 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Doherty et al. (Osteoarthritis and Cartilage, Vol. 6, pp. 153-160, 1998). Doherty teaches adenovirus vector-mediated gene transduction to human chondrocytes *in vitro*, wherein the adenovirus vector comprises a marker gene (abstract). Furthermore, the adenovirus lacks E1A, E1B, and E3 region (page 154).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 10, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Doherty et al. (Osteoarthritis and Cartilage, Vol. 6, pp. 153-160, 1998) taken with Arai et al. (J. Rheumatol, Vol. 24, pp. 1787-95,1997). Doherty teaches adenovirus vector-mediated gene transduction to human chondrocytes *in vitro*, wherein the adenovirus vector comprises a marker

gene (abstract). Furthermore, the adenovirus lacks E1A, E1B, and E3 region (page 154). However, Doherty does not specifically teach an adenovirus vector-mediated gene transduction to a primary human chondrocytes comprising delivering a recombinant adenovirus vector comprising a nucleic acid encoding an amino acid sequence that inhibits cartilage disease progression or that counteracts the loss of cartilage.

However, at the time the invention was made, Arai teaches adenovirus vector-mediated gene transduction to human chondrocytes *in vitro*, wherein the adenovirus vector comprises a nucleic acid sequence that encodes an amino acid sequence that inhibits cartilage disease progression, heat shock protein 70 and transforming growth factor beta-1 (TGF-beta1) (page 1788). Furthermore, the adenovirus lacks E1A, E1B, and E3 regions (page 1788).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Doherty taken with Arai to make and use a recombinant adenovirus comprising a nucleic acid encoding an amino acid sequence that inhibits cartilage disease progression to deliver said nucleic acid to primary human chondrocytes. One of ordinary skill in the art would have been motivated to combine the teachings to study the gene expression of TGF-beta1 in primary human chondrocytes using adenoviral mediated gene transduction.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 1, 11, and 24-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Doherty et al. (Osteoarthritis and Cartilage, Vol. 6, pp. 153-160, 1998) taken with Arai et al. (J.

Rheumatol, Vol. 24, pp. 1787-95, 1997) in further view of either Duprez et al. (IDS, Mechanism of Development, Vol. 57, abstract, 1996) or Noh et al. (US Patent No. 6,315,992).

The rejection of the base claims 1 and 24 under 103(a) is applied here as indicated above, Doherty in view of Arai. However, Doherty taken with Arai do not specifically teach an adenovirus vector-mediated gene transduction to a primary human chondrocytes comprising delivering a recombinant adenovirus vector comprising a nucleic acid encoding a bone morphogenesis protein (BMP).

However, at the time the invention was made, Duprez teaches that BMP are members of the growth factor beta (TFG-beta) superfamily, which are involved in a range of developmental processes. Over-expression of BMP-2 or BMP-4 led to a dramatic increase in the volume of cartilage elements. Furthermore, Noh teaches a method of treating cartilage using a vector comprising a nucleotide sequence encoding a member of the transformation growth factor superfamily, including BMP (column 3, lines 13-61).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Doherty taken with Arai in further view of either Duprez or Noh to make and use a recombinant adenovirus comprising a nucleic acid encoding a BMP to deliver said nucleic acid to primary human chondrocytes. One of ordinary skill in the art would have been motivated to combine the teachings to study the expression of BMP-2 or BMP-4 in primary human chondrocytes using adenoviral mediated gene transduction.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Application No.: 09/928,262

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [X] 7. Other: page 8 has an amino acid sequence with no corresponding SEQ ID NO:.

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

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